

Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative

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Accepted 10 July 2010
Published Online First
19 August 2010

ABSTRACT

Objective To develop evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis (UPIA).

Methods 697 rheumatologists from 17 countries participated in the 3E (Evidence, Expertise, Exchange) Initiative of 2008–9 consisting of three separate rounds of discussions and modified Delphi votes. In the first round 10 clinical questions were selected. A bibliographic team systematically searched Medline, Embase, the Cochrane Library and ACR/EULAR 2007–2008 meeting abstracts. Relevant articles were reviewed for quality assessment, data extraction and synthesis. In the second round each country elaborated a set of national recommendations. Finally, multinational recommendations were formulated and agreement among the participants and the potential impact on their clinical practice was assessed.

Results A total of 39 756 references were identified, of which 250 were systematically reviewed. Ten multinational key recommendations about the investigation and follow-up of UPIA were formulated. One recommendation addressed differential diagnosis and investigations prior to establishing the operational diagnosis of UPIA, seven recommendations related to the diagnostic and prognostic value of clinical and laboratory assessments in established UPIA (history and physical examination, acute phase reactants, autoantibodies, radiographs, MRI and ultrasound, genetic markers and synovial biopsy), one recommendation highlighted predictors of persistence (chronicity) and the final recommendation addressed monitoring of clinical disease activity in UPIA.

Conclusions Ten recommendations on how to investigate and follow-up UPIA in the clinical setting were developed. They are evidence-based and supported by a large panel of rheumatologists, thus enhancing their validity and practical use.

INTRODUCTION

In clinical practice, a large number of patients who present with recent-onset arthritis have

undifferentiated peripheral inflammatory arthritis (UPIA). In this context, patients' initial questions will focus on their likelihood of developing a well-defined rheumatic disease and on what the future holds for disease progression, persistence, functional impairment and quality of life. These are questions about future diagnosis and prognosis. The answers to these questions are vital for clinical decision making, including the choice of treatment.

The 3E Initiative (Evidence, Expertise, Exchange) in rheumatology is a multinational effort aimed at promoting evidence-based medicine by formulating practical recommendations addressing clinical problems.^{1–2} The objective of the 3E Initiative of 2008–9 was to develop practical recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis by integrating systematically generated evidence and expert opinion of a broad panel of international rheumatologists. Although the term 'inflammatory' in UPIA may seem redundant, the reason for its use was to clearly distinguish the target population from patients with degenerative joint disease, often called osteoarthritis or degenerative arthritis in the English medical literature.

METHODS

A total of 697 rheumatologists from 17 countries participated in the 3E Initiative of 2008–9. Each country was represented by a scientific committee consisting of one principal investigator and 5–13 members. The bibliographic team consisted of 10 international fellows (PM, IC, WK, RK, BK, MS, LS-F, KT, WV, EV) and five mentors (DA, LC, RL, DvdH, CB), one of the mentors also being the scientific organiser (CB). The 17 national principal investigators were selected and invited by the 3E scientific organiser (CB) and each national chair was in charge of composing a national steering committee. The experts were all the members of



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Recommendation

the 17 national steering committees who attended the multinational meetings for the 3E Initiative.

During the first international meeting (n=113 participants), 10 clinically relevant questions on how to investigate and follow-up UPIA were formulated and selected via a modified Delphi vote. The areas addressed were fourfold: (1) the phase prior to establishing the operational diagnosis of UPIA—namely, which differential diagnosis should be considered in a patient presenting with (inflammatory) arthritis and the minimal investigations necessary to consider a patient as having UPIA; (2) the diagnostic and prognostic value of clinical assessment and investigations in UPIA (history and physical examination, acute phase reactants, autoantibodies, x-rays, MRI, ultrasound (US), genetic markers and synovial biopsy); (3) the predictors of persistence (chronicity) in UPIA; and (4) the measures of clinical disease activity in UPIA.

The clinical questions were structured using the PIO format (Patients, Participants or Problem; Intervention or Index test; Outcomes or target conditions).³ The patients included 'adults with UPIA'. Duration of symptoms was not an exclusion criterion. The definition of UPIA is controversial and there is no widely accepted classification criterion for this condition. During the 2008–9 3E Initiative kick-off meeting, experts decided that only patients in whom clinically apparent joint swelling (synovial proliferation or synovial effusion) was observed by the rheumatologist should be included. For our review we systematically searched for studies of patients who did not fulfil diagnostic/classification criteria for any specific rheumatic disorder after initial assessment. Studies with mixed populations (eg, UPIA+arthralgia, UPIA+early rheumatoid arthritis (RA)) were also retained, as these could be useful for extrapolating results. The intervention or index test was defined according to each question (eg, erosions on x-rays, anti-citrullinated protein/peptide antibodies (ACPA) positivity) and the index test should have been assessed at baseline. The outcomes were defined as the development of well-defined rheumatic diseases (eg, RA, psoriatic arthritis) or relevant disease outcomes (eg, remission, radiographic progression). As diagnostic/classification criteria we accepted either internationally validated criteria (eg, American College of Rheumatology criteria for RA⁴) or the opinion of the treating physician/investigator.

A systematic literature search for articles published up to February 2009 was carried out in Medline, Embase and Cochrane Library using comprehensive search strategies elaborated in collaboration with experienced librarians. The searches were limited to diagnostic and prognostic studies using a modification

of published sensitive search strategies.^{5–8} No language restrictions were used. Retrieved citations were screened for titles, abstracts and full text using predefined inclusion and exclusion criteria; full read papers and review articles were hand-searched for additional references. Retained articles were graded for their methodological quality according to the levels of evidence of the Oxford Centre for Evidence-Based Medicine (<http://www.cebm.net/index.aspx?o=1025>).

Each question was addressed separately by independent searches. For each question, relevant data were extracted and appropriate statistics were calculated, including OR, sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios. Details and results of the literature search for each question will be published separately, while the current article describes the merging process between the evidence found for each question and the interpretation of this by the experts, having the 10 recommendations as the result.

In the second round, a national meeting was held in each country (total=697 participants) to discuss the generated evidence and propose a set of recommendations. In a third joint meeting the 17 scientific committees (n=94 participants) merged all propositions into 10 final recommendations via discussion and modified Delphi vote. The grade of recommendation according to the Oxford levels of evidence was attributed and the level of agreement was measured on a 10-point numerical rating scale (1=no agreement, 10=full agreement).⁹ Finally, the potential effect of each recommendation in clinical practice was assessed according to three impact statements voted by the rheumatologists.

RESULTS

A total of 39 756 references were identified, of which 250 were systematically reviewed (table 1). The 10 multinational key recommendations are listed in table 2 with the corresponding level of evidence and grade of recommendation. The mean level of agreement among the rheumatologists was 8.7 (range 7.4–9.1). The percentage of rheumatologists who indicated they would change their clinical practice according to each recommendation is shown in table 3. Evidence for repeating investigations was not found for any of the questions, therefore all recommendations about this topic were based on expert opinion.

Recommendation 1. *All possible causes of arthritis (idiopathic, autoimmune, degenerative, infectious, malignancy, traumatic, metabolic) should be considered in the differential diagnosis. Complete history and thorough physical examination will determine the ranking order of possible differential diagnoses. Investigations should be based on the differential diagnosis of the patient.*

Table 1 Results of the systematic literature search for each recommendation topic

Recommendation (number and topic)	Retrieved references by systematic literature search (n)	Articles included in the systematic reviews (n)
1. Pre-UIA differential diagnosis and investigations	540	51
2. History and physical examination	2914	37
3. Acute phase reactants	3699	18
4. Autoantibodies	13217	64
5. X-rays	3585	25
6.1. MRI	2595	11
6.2. Ultrasound	2111	2
7. Genetic markers	3109	26
8. Synovial biopsy	6536	4
9. Predictors of persistence (chronicity)	437	7
10. Measures of clinical disease activity	1013	5
Total	39756	250

UPIA, undifferentiated peripheral inflammatory arthritis.

Table 2 Multinational recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis

Recommendation (with level of evidence and grade of recommendation)	Agreement mean (SD)
1. All possible causes of arthritis (idiopathic, autoimmune, degenerative, infectious, malignancy, traumatic, metabolic) should be considered in the differential diagnosis. Complete history and thorough physical examination will determine the ranking order of possible differential diagnoses [5, D]. Investigations should be based on the differential diagnosis of the patient [5, D]	9.0 (1.7)
2. To establish a specific diagnosis and prognosis following presentation of UPIA, a careful systematic history and physical examination should be performed, with particular attention to age, gender [1a, A], geographical area [5, D], functional status [1a, A], duration of symptoms/early morning stiffness, number plus pattern of tender/swollen joints [1a, A], axial/enthesal involvement and extra-articular/systemic features [5, D]	8.8 (1.3)
3. ESR and CRP should be performed at baseline in the investigation for diagnosis [2b, B] and prognosis [2b, B] of UPIA and repeated when clinically relevant [5, D]	9.1 (1.4)
4. Testing of RF and/or ACPA should be performed in the evaluation of patients with UPIA, as these factors are predictive of RA diagnosis and prognosis; negative tests do not exclude progression to RA [1a, A]. If a connective tissue disease/systemic inflammatory disorder is suspected, additional autoantibody tests should be considered [5, D]	9.1 (1.2)
5. X-rays of affected joints should be performed at baseline [5, D]. X-rays of hands, wrists and feet should be considered in the evaluation of UPIA as the presence of erosions is predictive for the development of RA and persistence of disease [1a, A]. These should be repeated within 1 year [5, D]	7.4 (2.6)
6. There is insufficient evidence to recommend the routine use of MRI and US for diagnosis or prognosis in UPIA [5, D]; in UPIA and suspicion of RA, MRI of hands and wrists could be considered for diagnosis [2b, B]	8.2 (2.0)
7. There is no genetic test that can be routinely recommended [3b, D], however HLA-B27 testing may be helpful in specific clinical settings [5, D]	8.8 (1.5)
8. Routine synovial biopsy is not recommended but can give information for differential diagnosis, especially in patients with persistent monoarthritis [2b, B]	8.8 (1.8)
9. Predictors of persistent inflammatory arthritis should be documented and include disease duration of ≥ 6 weeks [1b, A], morning stiffness > 30 min [4, C], functional impairment [4, C], involvement of small joints [4, C] and/or knee [4, C], involvement of ≥ 3 joints [1b, B], ACPA [4, C] and/or RF positivity [4, C] and presence of radiographic erosion [1b, B]	8.6 (1.7)
10. Disease activity should be monitored [5, D], however no specific tool can be recommended [3b, C]	9.0 (1.7)

Values in square brackets indicate [level of evidence, grade of recommendation] according to the Oxford Centre for Evidence-based Medicine levels of evidence.

Agreement was voted on a scale from 1 to 10 (fully disagree to fully agree) by the 94 rheumatologists attending the 3E Multi-National Closing Meeting. These attendees were members of the 17 scientific committees involved in the 3E Initiative of 2008–2009.

ACPA, anti-citrullinated protein/peptide antibodies; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; UPIA, undifferentiated peripheral inflammatory arthritis; US, ultrasound.

Table 3 Percentage of rheumatologists in the 3E Initiative who indicated for each recommendation if it would change their clinical practice

Recommendation (number and topic)	The recommendation will change my practice (%)	The recommendation is already my practice (%)	I don't want to change my practice for this aspect (%)
1. Pre-UIPA differential diagnosis and investigations	0	96.5	3.5
2. History and physical examination	0	98.3	1.8
3. Acute phase reactants	5.4	91.1	3.6
4. Autoantibodies	1.8	96.4	1.8
5. X-rays	16.1	48.2	35.7
6. MRI and ultrasound	17.9	64.3	17.9
7. Genetic markers	1.8	92.9	5.4
8. Synovial biopsy	8.9	83.9	7.1
9. Predictors of persistence (chronicity)	24.6	66.7	8.8
10. Measures of clinical disease activity	12.3	84.2	3.5

UIPA, undifferentiated peripheral inflammatory arthritis.

As UPIA is an operational diagnosis after excluding well-defined rheumatic diseases, the question about pre-UIPA differential diagnosis and investigations was analysed by looking at the diagnosis that was excluded in cohorts of patients with UPIA and by identifying the inclusion and exclusion criteria of these studies as well as the investigations performed before the UPIA cohort was established. RA was the most frequent diagnosis reported as exclusion criterion^{10–59} and there was no standard baseline investigation undertaken prior to inclusion as UPIA (table 4).^{41–60}

Experts agreed that, when facing a new patient presenting with arthritis, every diagnosis needed to be kept in mind as UPIA is an exclusion diagnosis. Although the consensus was that it was impossible to name all possible diagnoses, it was felt useful to mention some major disease categories to make sure that these are considered. Experts also advised that UPIA should be constantly rethought, as patients may develop a disease that can be labelled with a specific diagnosis at any time. Moreover, this recommendation applies only if arthritis persists and not if it is self-limiting. Again, as the investigations will vary according to context and clinical presentation, experts felt that it would not be useful to make a list of recommended minimal investigations.

Recommendation 2. *To establish a specific diagnosis and prognosis following presentation of UPIA, a careful systematic history and physical examination should be performed with particular attention to age, gender, geographical area, functional status, duration of symptoms/early morning stiffness, number plus pattern of tender/swollen joints, axial/enthesal involvement and extra-articular/systemic features.*

Although selected observational studies were of good quality, there was large heterogeneity with respect to the type of history and physical examination features described.^{39 40 42–49 61–87} Of the quantified features, advanced age,^{44 83} female gender⁴⁴ and greater morning stiffness^{43 44} were predictive of an eventual diagnosis of RA. A higher number of tender⁴⁴ and swollen joints,^{43 44 61} involvement of small joints of hands and feet,^{44 83} involvement of both the upper and lower extremities⁴⁴ and symmetrical involvement⁴³ were also associated with progression to RA. Similar features were associated with disease persistence^{81–87} and development of erosions,^{48 63 78} while self-reported functional disability (Health Assessment Questionnaire (HAQ) score)^{67 76} and the presence of extra-articular features⁷⁶ were uniquely predictive of future disability, along with advanced age,^{67 76} female gender⁶⁷ and longer symptom duration.⁶⁷

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Table 4 Diagnosis reported as exclusion criteria and baseline investigations undertaken prior to inclusion as UPIA (ordered by the frequency of reporting in the retrieved literature), both in studies including patients exclusively with UPIA as well as in selected mixed populations that included a well-defined subset of patients with UPIA

A. Reported differential diagnosis prior to establishing the operational diagnosis of UPIA	
- Rheumatoid arthritis	- Polymyalgia rheumatica
- Osteoarthritis	- Lyme disease
- Spondyloarthritis (reactive arthritis, psoriatic arthritis, ankylosing spondylitis and undifferentiated spondyloarthritis)	- Vasculitis
- Crystal-related arthritis	- Juvenile inflammatory arthritis
- Trauma	- Palindromic rheumatism
- Connective tissue diseases (systemic lupus erythematosus, Sjögren syndrome and myositis)	- Fibromyalgia
- Septic arthritis	- Endocrinological origin
- Sarcoidosis	- Malignancy-related arthritis
- Soft tissue disorders	- Viral aetiology
B. Reported investigations prior to establishing the operational diagnosis of UPIA	
- History	- Microbiological assessment
- Tender and swollen joint count	- Anti-citrullinated protein/peptide antibodies
- Rheumatoid factor	- Radiography of the chest and/or of other affected joints
- C reactive protein	- Urinalysis
- Physical examination	- Thyroid function tests
- Hands and feet x-rays	- C3, C4
- Full blood count	- Immunoglobulins
- Antinuclear antibodies	- Antibodies to extractable nuclear antigens
- Erythrocyte sedimentation rate	- Antibodies to double-stranded DNA
- Biochemistry (liver function tests, glucose, urate and renal function)	- Specific serological assessment
- HLA typing (HLA-B27 and HLA-DR)	

UPIA, undifferentiated peripheral inflammatory arthritis.

Experts recognised the importance of the abovementioned evidence-based features and, based on their clinical experience, also highlighted the contribution of the patient's geographical area of residence, the presence of axial/enthesal involvement and the presence of extra-articular/systemic features. However, the greater relevance given to features included in the recommendation does not preclude the need to perform a careful systematic history and physical examination in every patient with UPIA.

Recommendation 3. *Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) should be performed at baseline in the investigation for diagnosis and prognosis of UPIA and repeated when clinically relevant.*

Elevated erythrocyte sedimentation rate (ESR) showed some diagnostic value for the development of RA^{74 85} but no prognostic value for persistence (chronicity) or structural damage.^{40 45 88} C reactive protein (CRP) appeared to be a poor predictor of persistent arthritis, radiological progression and functional disability.^{80 89} However, there was some evidence for the usefulness of elevated CRP in predicting RA, especially when the CRP levels are higher.^{48 88} In one study, CRP did not have any diagnostic value with regard to spondylarthropathy.³⁹ For other acute phase reactants, the evidence on diagnostic or prognostic value was scarce, negative or controversial.^{32 42 48 79 80 90–95}

Based on sparse evidence and on personal experience regarding acute phase reactants, experts recommended that only ESR and CRP should be performed at baseline and repeated according to the clinical setting.

Recommendation 4. *Testing of rheumatoid factor (RF) and/or ACPA should be performed in the evaluation of patients with UPIA, as these factors are predictive of RA diagnosis and prognosis; negative tests do not exclude progression to RA. If a connective tissue disease/systemic inflammatory disorder is suspected, additional autoantibody tests should be considered.*

The association of ACPA and rheumatoid factor (RF)^{11 42–44 48 50 73 96–110} with a diagnosis of RA at follow-up was compelling in the retrieved literature. The absence of ACPA or RF was diagnostically less helpful. The presence of ACPA or RF^{75 106–109 111–115}

also increased the probability of developing persistent synovitis or a worse radiographic outcome.^{73 75 84–86 116} For anti-keratin antibodies (AKA) and anti-perinuclear factor, the evidence suggests diagnostic usefulness; AKA also appears to have some prognostic value.^{11 96–99 107 110 114 117} For all other markers including a variety of other autoantibodies as well as bone and cartilage biomarkers, the evidence for diagnostic or prognostic value is scarce, negative or controversial.^{57 102 118–126} The same applies to disease outcomes different from those already mentioned.^{59 74 76 81 93 100 116 127 128}

The value of ACPA and RF in UPIA was recognised and, based on clinical experience, experts also advised consideration of additional autoantibody tests if non-RA systemic inflammatory disorders are suspected. The use of the general term ACPA was preferred as the literature describes several tests for detecting antibodies to citrullinated peptides (such as anti-CCP1 and anti-CCP2) and newer generation tests are also expected to be used in the future.

Recommendation 5. *X-rays of affected joints should be performed at baseline. X-rays of hands, wrists and feet should be considered in the evaluation of UPIA as the presence of erosions is predictive for the development of RA and persistence of disease. These should be repeated within 1 year.*

Radiographic erosions^{43 49} and Larsen grade 1 (in a population without erosions at baseline)²⁰ increased the probability of developing RA from UPIA. Moreover, when comparing mild versus progressive disease after 1 year follow-up, Sharp/van der Heijde scores at baseline were significantly higher in the progressive disease group.⁴⁸ In another study,⁴⁴ erosions were found to be a predictor of RA in univariate but not in multivariate analysis.

Overall, studies in mixed populations also provided some evidence for the usefulness of x-rays in predicting RA.^{72 88 92 109 122 129–135} In general, prognosis was worse when radiographic abnormalities at baseline were more severe.^{75 91 109 116 133 136–140}

Experts recognised the clinical value of hand and feet x-rays in UPIA and, based on clinical experience, also recommended that x-rays of affected joints should be performed at baseline;

furthermore, experts advised that x-rays should be repeated within 1 year (in case of disease persistence). Moreover, although not voted to be included in the recommendation, some of the experts expressed their opinion that pelvic/sacroiliac joint x-rays should also be considered, particularly in RF- and ACPA-negative patients or if spondyloarthritis is suspected.

There was a slightly lower agreement about this recommendation (table 2, 7.4 agreement), with a larger proportion of experts stating that they did not want to change their practice for this aspect (table 3, 35.7%). This lower concordance was mainly related to the inclusion of 'x-rays of affected joints at baseline' and about the advice to repeat x-rays 'within 1 year'.

Recommendation 6. *There is insufficient evidence to recommend the routine use of magnetic resonance imaging (MRI) and ultrasound (US) for diagnosis or prognosis in UPIA; in UPIA and suspicion of RA, MRI of hands and wrists could be considered for diagnosis.*

Bone oedema was found to be an independent predictor of the future development of RA from UPIA,¹⁴¹ and the presence of a distinct MRI synovitis and erosion pattern with the involvement of several hand joints but not the first carpometacarpal joint also increased the probability of developing RA.²⁰ The absence of the same MRI synovitis pattern decreased the probability of developing RA.²⁰ Overall, MRI studies in mixed populations^{101 134 142–147} provided some evidence for the usefulness of MRI (bone oedema, synovitis and erosions) in predicting RA. Regarding US, two mixed populations revealed US-power Doppler signal and US-gray scale synovitis as potential candidates for future studies in UPIA.^{148 149}

Experts recognised that MRI of the hands and wrists has already been shown to be useful in predicting the development of RA from UPIA, while the value of US in UPIA is still to be determined. However, data are still too scarce to recommend the routine use of any of these imaging tools. This recommendation does not dispute the fact that, compared with physical examination and x-rays, both MRI and US may offer advantages through more sensitive depiction of inflammatory and destructive disease manifestations. The current recommendation pertains only to the diagnostic and prognostic value of these imaging tools in UPIA.

Recommendation 7. *There is no genetic test that can be routinely recommended, however HLA-B27 testing may be helpful in specific clinical settings.*

There was a great heterogeneity among the genetic markers tested.^{39 40 46 50–52 65 84 127 133 150–165} The shared epitope (SE) was the most frequently studied marker. Eight studies^{40 50 65 133 153–155 158} tested its diagnostic utility and showed poor results. Only in one study was the positive likelihood ratio for RA relevant, but this result came from the study with the poorest quality and smallest sample size.⁴⁰ In isolation, no other genetic marker was informative of a future diagnosis in patients with UPIA. With regard to prognosis, the SE was weakly associated with a poor prognosis of arthritis in terms of development of erosions, mortality, disability and persistent synovitis.^{65 127 133 163 164} Other genes were not good predictors of erosions or other less studied outcomes.

The experts acknowledged the current lack of evidence for the practical utility of genetics in UPIA. However, based on their clinical experience, experts chose to highlight that HLA-B27 may be helpful in the appropriate clinical setting—namely, when spondyloarthritis is suspected.

Recommendation 8. *Routine synovial biopsy is not recommended but can give information for differential diagnosis, especially in patients with persistent monoarthritis.*

Studies had significant clinical and statistical heterogeneity.^{22 23 166 167} Three broad synovial features of interest were identified in the literature: ACPA staining, immunohistochemistry and vascular patterns. In contrast to serological ACPA testing, ACPA staining was shown not to be highly specific for a diagnosis of RA.¹⁶⁷ In one study, synovial histopathology seemed to differentiate between RA and non-RA.¹⁶⁶ The vascular pattern in undifferentiated arthritis was not specific enough to differentiate between spondyloarthritis and RA.^{22 23}

The exact role of synovial biopsy in UPIA is yet to be determined and experts felt that it could not be recommended as a routine procedure. However, experts also highlighted the fact that synovial biopsy may give important diagnostic clues, especially in some selected cases (eg, persistent/chronic refractory monoarthritis, suspicion of malignancy or suspicion of chronic infection such as tuberculosis).

Recommendation 9. *Predictors of persistent inflammatory arthritis should be documented and include disease duration of ≥6 weeks, morning stiffness >30 min, functional impairment, involvement of small joints and/or knee, involvement of ≥3 joints, ACPA and/or RF positivity and presence of radiographic erosion.*

The question about chronicity was investigated by looking at prognostic studies that used multivariate analysis to identify independent predictors of persistence (chronicity). At baseline the following variables were found to be independent predictors of persistent (inflammatory) arthritis: disease duration,^{75 82 116} duration of morning stiffness,^{75 85 86} change of functional status (measured by HAQ) in the first 3 months,⁸² failure to respond 2 weeks after local treatment with intra-articular corticosteroids,⁸² small joint involvement,¹⁶⁸ knee involvement,⁸⁵ presence of RF,^{75 85} presence and level of ACPA,^{75 86 168} functional status (HAQ),¹⁶⁹ arthritis of at least three joints,⁷⁵ proximal interphalangeal joint involvement,¹⁶⁹ metatarsophalangeal joint involvement⁷⁵ and radiographic erosion at the hands and feet.⁷⁵ The magnitude of the association in the same predictor was diverse among the studies depending on the patient characteristics (namely, if the population was purely UPIA or not), the study design and the variables used to adjust for in the models.

Recommendation 10. *Disease activity should be monitored, however no specific tool can be recommended.*

Five studies evaluated the validation of different clinical measures in patients with UPIA. Validation aspects of four questionnaires (WHO Disability Assessment Schedule,¹⁷⁰ London Handicap Scale, Disease Repercussion Profile and the HAQ¹⁷¹) and three physical measures (RA Disease Activity Index,¹⁷² McGill Range of Motion Index¹⁷³ and NOAR Damage Joint Count¹⁷⁴) were partially assessed in these studies but none of the instruments of disease activity was fully validated for its use in UPIA.

Although no instrument of disease activity has been fully validated for its use in UPIA, experts felt that it was important to recommend that there should be a conscious effort to record disease activity.

DISCUSSION

Ten multinational recommendations on how to investigate and follow-up UPIA in the clinical setting were developed, which are practical, evidence-based and supported by a large panel of international rheumatologists in the 3E Initiative.

We followed an established group decision method. A representative expert panel of 697 academic and community rheumatologists from 17 countries selected relevant questions that reflect the challenges of approaching a patient with UPIA. They

openly discussed the evidence from the literature followed by a silent voting process. We used the touch pad methodology with prespecified cut-off levels of agreement to generate the final recommendations. Several rounds of rewording and revoting were sometimes required to reach the specified cut-off for agreement. This process highlights the international dimension of this collaboration and strengthens the current recommendations.^{1 2} It ensured that the final recommendations were evidence-driven as well as clinically relevant.

Furthermore, the broad participation increases external validity and enhances future dissemination and implementation into rheumatological practice worldwide. Another main feature of the 3E Initiative was the promotion of epidemiology and systematic literature research, all participants having been updated on how to appraise published evidence.

There is widespread interest in predictive medicine. Following a strict methodology, we aimed to find all available evidence regarding each question which resulted in a large number of reviewed articles. However, the evidence in truly UPIA populations is scarce, exposing the need to create a research agenda addressing this topic. In particular, future studies should clearly distinguish between individuals with early well-defined rheumatic diseases, individuals with UPIA and individuals with inflammatory joint symptoms but no obvious joint swelling. All these populations can be studied for predictive algorithms and results may be different depending on the study population.

The definition of UPIA is controversial and much of the literature is skewed towards early RA. The difficulty in defining UPIA is underlined by the continuous changing face of different categories of patients, which can be well illustrated by the recent new ACR/EULAR criteria for RA,¹⁷⁵ as several of the patients we now describe as having UPIA will likely be labelled as having RA. Nevertheless, despite the influence that this changing may have on research and daily practice, the recommendations presented in this article are based on currently available evidence. They may help the clinician in the effective management of patients with UPIA and can be adjusted if future studies or clinical experience reveal new insights.

In summary, multinational recommendations for the investigation and follow-up of patients with undifferentiated arthritis in daily clinical practice were developed, integrating systematic literature review and expert opinion with the aim of promoting evidence-based medicine and ultimately improving patient care.

Acknowledgements The authors thank all members of the 3E scientific committees, all participants of the national meetings, the support from Margaux Orange and the librarians who helped in elaborating the systematic literature searches. CB holds a Canada Research Chair in Knowledge Transfer for Musculoskeletal Care.

Funding This work was supported by Abbott with an unrestricted educational grant.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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